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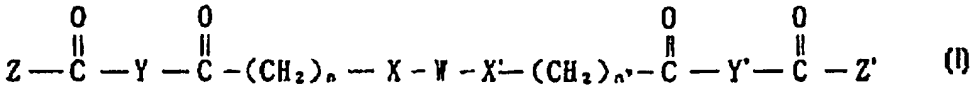
添付公開書類
国際調査報告書

(54)Title: TRYPTASE INHIBITOR

(54)発明の名称 トリプターゼ阻害剤

Bifunktionelle Tryptase-Inhibitoren



(I)

(57) Abstract

Compounds represented by general formula (I) (wherein each symbol is as defined in the specification) or pharmacologically acceptable salts thereof, a pharmaceutical composition thereof, and use thereof as a pharmaceutical. The compounds and pharmacologically acceptable salts thereof have an excellent tryptase inhibitory activity, are orally administrable, and have a reduced toxicity, thus being useful for pharmaceuticals, for example, those for prophylaxis or therapy of allergic diseases and the like.

No

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/03978

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07D307/85, C07D405/06, C07D495/04, C07D333/66, A61K31/38, A61K31/34, A61K31/445, A61K31/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07D307/85, C07D405/06, C07D495/04, C07D333/66, A61K31/38, A61K31/34, A61K31/445, A61K31/54

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 95/32945, A1 (ARRIS PHARMACEUTICAL COOPERATION), 7 December, 1995 (07. 12. 95) & EP, 763016, A1 & JP, 10-501238, A	1-9
A	WO, 96/09297, A1 (ARRIS PHARMACEUTICAL COOPERATION), 28 March, 1996 (28. 03. 96) & EP, 782571, A1 & JP, 10-506390, A	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December, 1998 (14. 12. 98)	22 December, 1998 (22. 12. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

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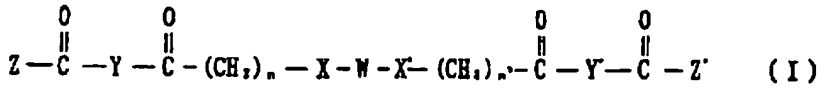
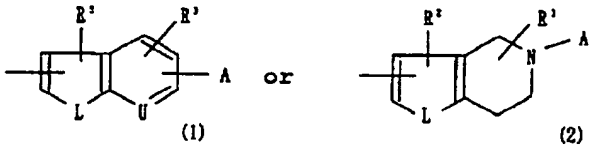
Scope of the patent claims

1. Compound represented by the formula (I) below, or pharmacologically acceptable salt thereof



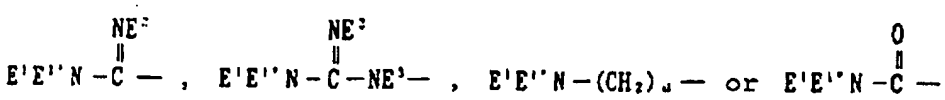
(I)

{in the formula, Z and Z' represent

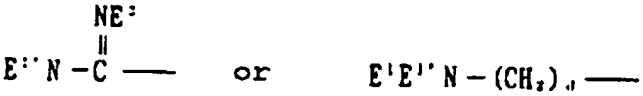


(1) (2)

[where A represents



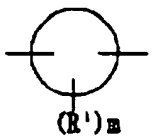
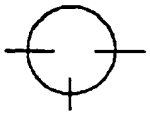
(E^1, $E^{1'}$, E^2 and E^3 represent hydrogen or an aralkyl or alkyl group, or a protective group with respect to amidino, guanidino or primary amino groups, and may be identical or different, E^2 may also represent a hydroxyl group, and E^1 and $E^{1'}$ may together form a heterocycle optionally containing a heteroatom; and d represents an integer from 1 to 3; where when Z and/or Z' are formula (2), A represents



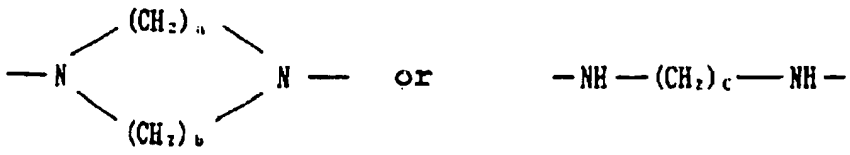
(where d is 2 or 3); L represents —O—, —NR^4—, —S—, —SO_2— or —CH_2— (where R^4 represents hydrogen or an alkyl, cycloalkyl, aralkyl or acyl group); U represents

=CH— or =N—

and R^2 and R^3 represent hydrogen, a halogen, or an alkyl, trifluoromethyl, hydroxyl, amino, acyl or alkoxy group, and may be identical or different] and may be identical or different; W represents

$-(CH_2)_l-$ (in the formula, l represents an integer from 1 to 10), or  (in the formula, 

represents a cycloalkylene group of from 3 to 14 carbon atoms, a heterocycloalkylene group of from 3 to 14 carbon atoms, an arylene group or a heteroarylene group; R^1 represents hydrogen, a halogen, or an alkyl, trifluoromethyl, hydroxyl, amino, acyl or alkoxy group; and m represents 0 or an integer from 1 to 4); X and X' represent oxygen, $-NR^5-$ (where R^5 represents hydrogen or an alkyl, cycloalkyl, aralkyl or acyl group) or a direct bond, and may be identical or different; and Y and Y' represent

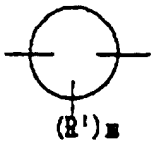


(where a and b represent an integer from 1 to 3 and may be identical or different, and c represents an integer from 1 to 8) and may be identical or different; and n and n' represent 0 or 1 and may be identical or different}.

2. Compound or pharmacologically acceptable salt thereof as claimed in claim 1, where Z and Z' are formula (I).

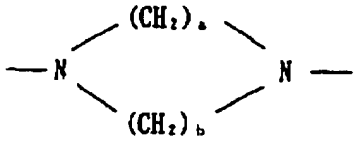
3. Compound or pharmacologically acceptable salt thereof as claimed in claim 1, where Z and Z' are formula (II).

4. Compound or pharmacologically acceptable salt thereof as claimed in claim 1, where W is



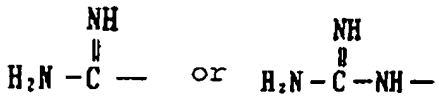
(in the formula, each symbol is as defined above).

5. Compound or pharmacologically acceptable salt thereof as claimed in claim 1, where Y and Y' are



(in the formula, each symbol is as defined above).

6. Compound or pharmacologically acceptable salt thereof as claimed in claim 1, where A is



7. Pharmaceutical composition containing as effective component a compound or pharmacologically acceptable salt thereof as claimed in claim 1.

8. Tryptase inhibitor containing as effective component a compound or pharmacologically acceptable salt thereof as claimed in claim 1.

9. Anti-allergy agent based on tryptase inhibition, containing as effective component a compound or pharmacologically acceptable salt thereof as claimed in claim 1.

Working Example 1: Synthesis of cis-1,5-bis[4-(5-amidinobenzofuran-2-ylcarbonyl)piperazinyl-1-yl-carbonylmethyloxy]cyclooctane dihydrochloride

Working Example 2: Synthesis of 1,4-bis[4-(5-amidinobenzofuran-2-ylcarbonyl)piperazinyl-1-yl-carbonylmethyloxy]benzene dihydrochloride

Working Example 5: Synthesis of cis-1,5-bis[4-(5-amidinobenzofuran-2-ylcarbonyl)piperazinyl-1-yl-carbonyloxy]cyclooctane dihydrochloride

Working Example 10: Synthesis of 1,4-bis[4-[5-amidino-4,5,6,7-tetrahydrothieno[3,2-C]pyridin-2-yl-carbonyl]piperazinyl-1-ylcarbonylmethyloxy]benzene diacetate

Working Example 22: Synthesis of 1,5-bis[4-(5-amidinobenzofuran-2-ylcarbonyl)piperazinyl-1-yl]azelaic acid amide ditrifluoroacetate